CLAIMS

1. A method of identifying, screening, characterising or designing a chemical entity which mimics or binds to FIH, which method comprises comparing a structural model of FIH with a structural model for said chemical entity, wherein said structural model of FIH is derived from structural factors or structural coordinates determined by subjecting to X-ray diffraction measurements a crystal comprising FIH.

2. Use of the structural co-ordinates obtainable by subjecting a crystal comprising FIH to X-ray diffraction measurements and deducing the structural co-ordinates from the diffraction measurements, to identify, screen, characterise, design or modify a chemical entity.

3. A method or use according to claim 1 or 2 in which the structural coordinates are those shown in Table 3.

4. A method or use according to any one of the preceding claims, wherein said chemical entity binds to FIH.

5. A method or use according to any one of the preceding claims, wherein said chemical entity is selected to inhibit the asparaginyl hydroxylase activity of FIH.

6. A method or use according to any one of the preceding claims further comprising contacting said chemical entity with HIF or a fragment thereof or a homologue of either thereof incorporating asparagine 803 with FIH or a homologue thereof which maintains the asparaginyl hydroxylase activity of FIH and monitoring for hydroxylation of asparagine 803.

7. A chemical entity identified by a method for use according to any one of the preceding claims, wherein said chemical entity inhibits the asparaginyl hydroxylase activity of FIH.

8. A chemical entity according to claim 7 wherein said chemical entity inhibits hydroxylation of the asparagine position 803 of HIF by FIH.

9. A chemical entity according to claim 7 wherein said chemical entity inhibits dimerisation of FIH.

10. A chemical entity according to claim 9 wherein said chemical entity binds to residues that form the dimerisation interface of FIH, selected from residues 330 to 346 of FIH.

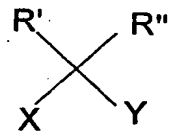
11. A chemical entity according to claim 7 wherein said chemical entity binds to iron, or prevents Fe(II) binding to FIH.

12. A chemical entity according to claim 11, wherein said chemical entity is a compound selected from a thiol, alcohol, phenol, carboxylate, hydroxamate, imidazole or other heterocyclic compound, that binds to iron.

13. A chemical entity according to claim 7 wherein said chemical entity disrupts 2-oxoglutarate binding to FIH.

14. A chemical entity according to claim 13, wherein said chemical entity is R-entiomer of N-oxaloylalanine, procollagen prolyl-hydroxylase and a PHD isozyme.

15. A chemical entity according to claim 13, wherein said chemical entity is a compound of the formula

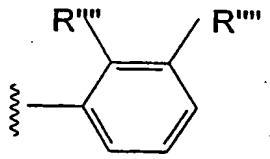


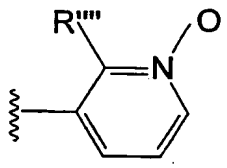
(I)

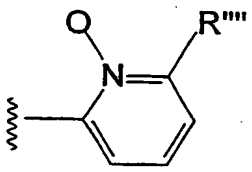
wherein each of R′ and R", which may be the same or different, is H, F or C_1 to C_3 alkyl or substituted alkyl, CH_2OH, CH_2CO_2H or $CONH_2$, X is COOH, SOOH, or CONHH or an ester thereof, or other group which forms a favourable interaction with one or more of the side chains of Lys-214, Thr-196 and Tyr-145,

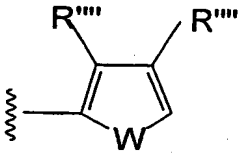
Y is - $(CR'''R''')_nZ$, where Z is

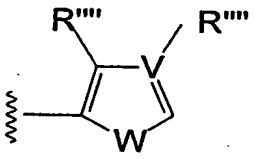
- NR'''COCOOH, -NR'''CSCOOH, - NR'''COCOSH, - CHSR'''CONR'''R'''', -CHOR'''CONR'''OR''', - CHSR'''CONR'''OR''' or - CHOR'''CONR'''NR'''OR''', wherein each R''', which may be the same or different, is H, alkyl, OH or O-alkyl, n is 0 to 3, or











wherein R'''' is OH, OR''' or NHCOR''', and W is S, NH, or O;

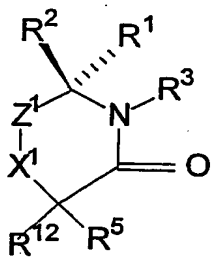
16. A chemical entity according to claim 13 or 15 wherein said chemical entity interferes with the interactions at residues 214, 196 and 145 of FIH, or which interrupts the interactions of 2OG with residues 281, 186, 188, 207 or 196 of FIH.

17. A chemical entity according to claim 16 wherein said chemical entity interrupts binding of FIH for Asn 803 of HIF, preferably, by interfering with binding of HIF at residues 102, 239 or 238 of HIF.

18. A chemical entity according to claim 17 which interferes with Site 1 binding of CAD of HIF to FIH and which exploits electrostatic, hydrogen binding and/or hydrophobic interactions with one or more residues selected from 102, 104, 106, 201, 202, 147, 239, 299-303, 313, 317, 318, 321, 324, 238, 296 or 321 to 324 of FIH.

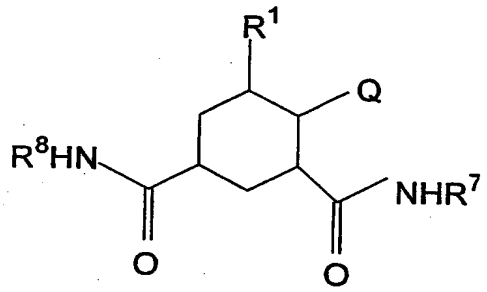
19. A chemical entity according to claim 17 wherein said chemical entity interferes with binding of CAD of HIF to FIH at Site 2, and exploits electrostatic, hydrogen binding and/or hydrophobic interactions with residues 149, 150, 151, 152, 159, 162, 163, 167, 181, 182 ,183, 184 or 185.

20. A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula

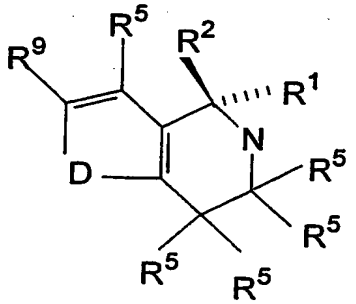


II

21. A chemical entity according to claim 17, wherein said chemical entity is a compound of the formula



22. A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula



IV

23. A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula

X[B]-[C]

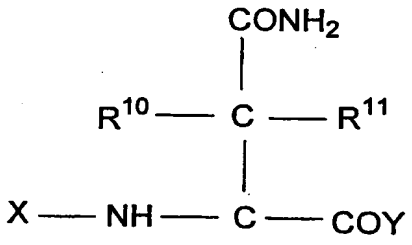
where X is as defined above, B is a linker group and C is an entity binding to part of the CAD binding site of FIH;

24. A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula

X-[B]-[E]

where X and B are as defined above and E is an entity binding to part of the CAD when bonded to HIF.

25. A chemical entity according to claim 7 wherein said chemical entity is a compound of the formula



wherein X represents a valine residue or an analogue thereof and Y represents an alanine residue or an analogue thereof, R^{10} is fluorine or C_1 - C_3 alkyl, and R^{11} is fluorine, C_1 - C_3 alkyl or hydrogen or a corresponding compound R^{11} is absent or R^{10} and R^{11} form a methylene group.

26. A chemical entity according any of one of claims 7 to 25 for use in a method of treatment.

27. A chemical entity according to any of claims 7 to 25 for use in the treatment of a condition associated with increased or decreased HIF levels or activity or the treatment of a condition where it is desired to modulate HIF activity.

28. A chemical entity according to claim 27 wherein said condition is ischaemia, wound healing, auto-, allo- or xeno-transplantation, systemic high blood pressure, cancer or an inflammatory disorder.